nitrogen, phosphorous or silicon atoms;
where an aryl moiety is a mono- or polycyclic unsaturated moiety having 3-14 carbon atoms; and
where a heteroaryl moiety is a mono- or polyheterocyclic unsaturated moiety having 3-14 carbon atoms;
or a pharmaceutically acceptable salt, ester, carbamate, metabolite or pro-drug thereof;
or a pharmaceutically acceptable salt of such ester or carbamate.

42. **(Once amended)** A method for producing a compound of claim 1 which comprises contacting a homologous C28 epimer with a titanium tetraalkoxide reagent under suitable conditions and for a sufficient time to permit epimerization.

45. **(Once amended)** The method of any of claims 42-44 wherein the homologous C28 epimer is rapamycin.

Remarks

Applicants respectfully submit that the present Amendment and following Remarks remove all grounds for rejection of the application, thereby placing it in condition for allowance.

Election/Restriction:

Method of making claims 42 and 45 have been amended to have the same scope as compound claim 1. These amendments are supported by the application as filed, e.g., see page 2, line 10 – page 3, line 2 and page 35, lines 11-18. Since claims 42-45 are now of the same scope as claim 1, Applicants respectfully request that these claims be examined together.

Rejection of claims 1-41 under 35 U.S.C. §112, second paragraph:

Claims 1-41 remain rejected under 35 U.S.C. §112, second paragraph, as being indefinite. In particular, the Examiner states that the metes and bounds of the phrase "substituted or unsubstituted aliphatic or acyl moiety"; the terms "heteroaliphatic", "aryl", and "heteroaryl"; and the phrase "pharmaceutically acceptable derivative" are not known. Applicants respectfully traverse these rejections.

The purpose of the claim definiteness requirement is to (a) ensure that the scope of the claims is clear so that the public is informed of the boundaries of what constitutes infringement

of the patent and (b) provide a clear measure of what Applicants regard as the invention so that it can be determined whether the claimed invention meets all the criteria for patentability. MPEP §2173. No more is required.

Applicants have acknowledged that some of the terms and phrases used in the pending claims are broad; however, as noted in previous responses, it is well accepted that breadth of a claim is not to be equated with indefiniteness. *In re Miller*, 441 F.2d (CCPA 1971). In particular, if the scope of the subject matter embraced by the claims is clear, and if Applicants have not otherwise indicated that they intend the invention to be of a scope different from that defined in the claims, then the claims comply with 35 U.S.C. §112, second paragraph. MPEP §2173.04.

Substituted or unsubstituted aliphatic or acyl moiety

The phrase "substituted or unsubstituted aliphatic or acyl moiety" clearly encompasses *all* aliphatic and acyl moieties irrespective of whether these are substituted and irrespective of the nature of any substituents. Regarding "acyl moieties", *any* R group may be present in the generic formula RCO-. The broad scope is supported by the specification (e.g., see page 5, line 10-22; page 6, line 27 – page 7, line 6; and page 30, line 34 – page 31, line 34). There is no indication that Applicants intended this phrase to have a narrower scope. There is also no doubt that those having ordinary skill in the art can tell whether a particular moiety is an aliphatic or acyl moiety.

Accordingly, there is no reason to believe that a person of ordinary skill in the art would not be able to determine whether a particular compound lies within or outside the scope of claims that include the phrase. No more is required to satisfy the claim definiteness requirement – the rejection should therefore be removed.

The Examiner argues, in this context, that one skilled in the art cannot say which substituents (i.e., which "substituted or unsubstituted aliphatic or acyl moieties") are permitted at positions R^{28}, R^{43} and R^{7} (where R^{A} and R^{B} are involved). The Examiner relies on Applicants' general statement that seemingly small structural changes in rapamycin often cause dramatic changes in chemical properties. As the Examiner put it, "Applicants need to say which substituents work because "any" group would not be expected to have the same property."

Applicants are confused by the Examiner's argument. In particular, what does the Examiner mean by "which substituents *work*"? Is the Examiner suggesting that substituents at positions R^{28}, R^{43} and R^{7} should be limited to those that produce compounds with the same properties or uses? What is the Examiner's statutory basis for such a requirement? Applicants have invented a method for preparing an entirely new class of compounds (e.g., see page 2, lines 10 – page 3, line 16). The absence of prior art rejections reflects this. Claims 1-41 are directed to this new class of compounds and claims 42-45 are directed to a method for making these. Claims 1-45 are in no way limited to compounds with specific properties and/or uses. The fact that compounds with one type of substituent may have different properties from compounds with another type of substituent does not mean that some of those substituents do not "work". Moreover, not all of the claimed compounds need to, or would be expected to, have the *same* properties or uses. In fact, the specification explicitly states that the compounds of this invention are useful for a number of different applications (e.g., see pages 63-66). For example, certain compounds may have antifungal activity. In some cases compounds with immunosuppressive activity are desired. In other cases the opposite is true (e.g., for regulated gene therapy applications). Each case involves compounds with substituents which "work". Clarification or removal of the Examiner's rejection is requested.

Heteroaliphatic, aryl and heteroaryl

As discussed by Applicants in response to the previous Office Action, the terms "heteroaliphatic", "aryl" and "heteroaryl" are explicitly and clearly defined in the specification as filed (see page 32, lines 1-4 and 8-10). There is no indication that Applicants intended these terms to have a different scope. Further, there is no doubt that those of ordinary skill in the art can recognize compounds that include the defined moieties.

Accordingly, there is no reason to believe that one having ordinary skill in the art would not be able to determine whether a particular compound lies within or outside the scope of claims that include these terms. No more is required to satisfy the claim definiteness requirement. However, despite this, claims 1 and 20 have been amended in order to expedite prosecution of this case towards allowance. In particular, the definitions of "heteroaliphatic", "aryl" and "heteroaryl" found on page 32 of the specification have been incorporated into claims 1 and 20. These amendments are made without prejudice, without intent to abandon any original claimed

subject matter, and without intent to acquiesce in any rejection of record. Applicants reserve the right to file one or more continuing applications containing the unamended claims. Applicants respectfully submit that the metes and bounds of the terms "heteroaliphatic", "aryl" and "heteroaryl" are now clearly and explicitly stated within the claims. The rejection should be withdrawn.

Pharmaceutically acceptable derivative

Again, as discussed by Applicants in response to the previous Office Action, the phrase "pharmaceutically acceptable derivative" is explicitly and clearly defined in the specification as filed (see page 30, lines 23-33). However, despite this, claims 1 and 20 have been amended in order to expedite prosecution of this case towards allowance. In particular, both claims 1 and 20 have been amended to read "or a pharmaceutically acceptable salt, ester, carbamate, metabolite or pro-drug thereof; or a pharmaceutically acceptable salt of such ester or carbamate". Again, these amendments are being made in order to expedite prosecution of this case towards allowance. These amendments are made without prejudice, without intent to abandon any original claimed subject matter, and without intent to acquiesce in any rejection of record. Applicants reserve the right to file one or more continuing applications containing the unamended claims.

Applicants respectfully submit that those of ordinary skill in the art can readily recognize a pharmaceutically acceptable salt, ester, carbamate, metabolite or pro-drug of a claimed 28-epirapalog; or a pharmaceutically acceptable salt of such ester or carbamate. Accordingly, there is no reason to believe that one having ordinary skill in the art would not be able to determine whether a particular compound lies within or outside the scope of claims 1-41. No more is required to satisfy the claim definiteness requirement. The rejection should be withdrawn.

Further, for the sake of completeness, Applicant notes that the Examiner seems to have misunderstood the comments that were made in response to the previous Office Action regarding the pyrano question, namely:

> "The Examiner asks whether a pyrano derivative would or would not be a pharmaceutically acceptable derivative under the claim. Applicant respectfully submits

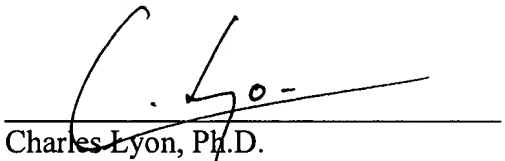
that it would be if, upon administration to a patient, it is capable of providing a 28-epirapalog as described; otherwise it would not be."

Applicants were not suggesting that pyran *itself* would be a pharmaceutically acceptable derivative of a claimed 28-epirapalog, but that a pyrano *derivative* of a claimed 28-epirapalog would be if, upon administration to a patient, it is capable of providing a claimed 28-epirapalog. Applicants hope that this clarifies the issue.

Conclusion

As required, attached hereto as **Appendix A** is a marked-up version of the changes made to the claims by the present Amendment. For the reasons presented above, it is submitted that as amended the claims are allowable over the art of record. Please charge any fees that may be required, or credit any overpayment, to our Deposit Account No. 03-1721.

Respectfully submitted,



Charles Lyon, Ph.D.
Agent for Applicant
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2-26-03 Linda M. Amato

Date Signature

Linda M. Amato

Typed or Printed Name of person signing certificate

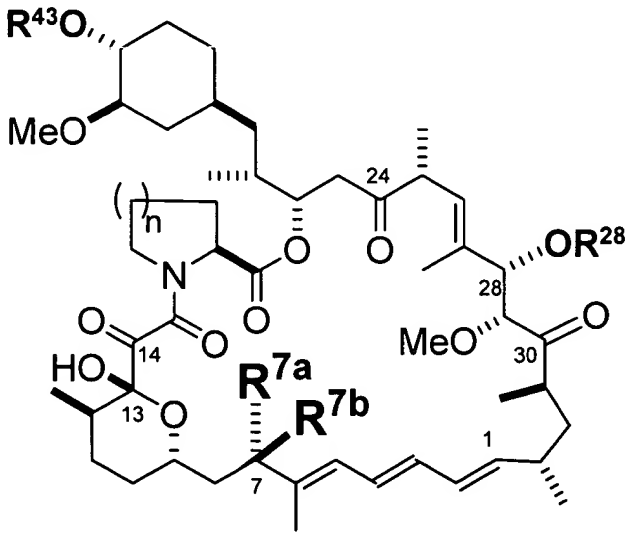
APPENDIX A

VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the claims:

Claims 1, 20, 42 and 45 have been amended as follows:

1. **(Twice amended)** A compound of the formula:

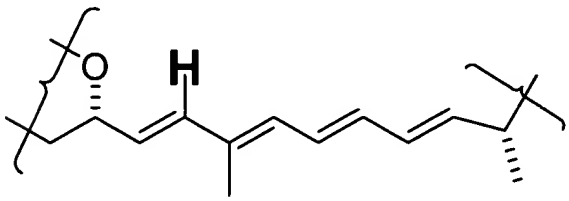


wherein

n is 1 or 2;

R^{28} and R^{43} are independently selected from the group consisting of H and a substituted or unsubstituted aliphatic or acyl moiety;

one of R^{7a} and R^{7b} is H and the other is halo, $-R^A$, $-OR^A$, $-SR^A$, $-OC(O)R^A$, $-OC(O)NR^AR^B$, $-NR^AR^B$, $-NR^BC(O)R^A$, $-NR^BC(O)OR^A$, $-NR^BSO2R^A$, or $-NR^BSO2NR^AR^{B'}$; or R^{7a} and R^{7b} taken together, are H in the tetraene moiety:



where R^A is H or a substituted or unsubstituted aliphatic, heteroaliphatic, aryl, or heteroaryl moiety; ~~and~~

where R^B is H, OH or a substituted or unsubstituted aliphatic, heteroaliphatic, aryl, or heteroaryl moiety;

where a heteroaliphatic moiety is an aliphatic moiety which contains one or more oxygen, sulfur, nitrogen, phosphorous or silicon atoms;

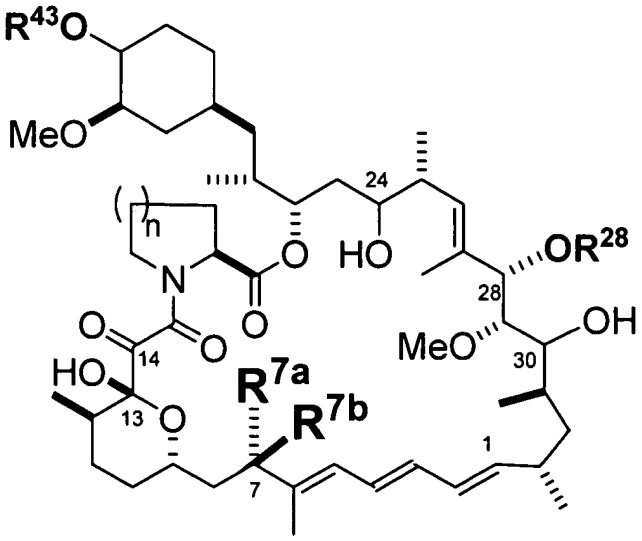
where an aryl moiety is a mono- or polycyclic unsaturated moiety having 3-14 carbon atoms; and

where a heteroaryl moiety is a mono- or polyheterocyclic unsaturated moiety having 3-14 carbon atoms;

or a pharmaceutically acceptable ~~derivative thereof~~ salt, ester, carbamate, metabolite or pro-drug thereof;

or a pharmaceutically acceptable salt of such ester or carbamate.

20. **(Twice amended)** A compound of the formula:

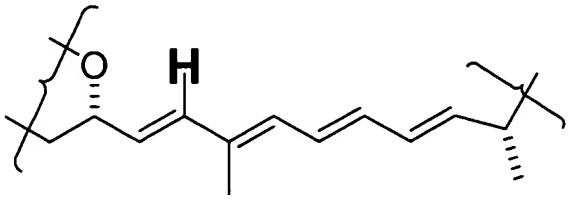


wherein

n is 1 or 2;

R^{28} and R^{43} are independently selected from the group consisting of H and a substituted or unsubstituted aliphatic or acyl moiety;

one of R^{7a} and R^{7b} is H and the other is halo, $-R^A$, $-OR^A$, $-SR^A$, $-OC(O)R^A$, $-OC(O)NR^AR^B$, $-NR^AR^B$, $-NR^BC(O)R^A$, $-NR^BC(O)OR^A$, $-NR^BSO2R^A$, or $-NR^BSO2NR^AR^{B'}$; or R^{7a} and R^{7b} taken together, are H in the tetraene moiety:



where R^A is H or a substituted or unsubstituted aliphatic, heteroaliphatic, aryl, or heteroaryl moiety; ~~and~~

where R^B is H, OH or a substituted or unsubstituted aliphatic, heteroaliphatic, aryl, or heteroaryl moiety;

where a heteroaliphatic moiety is an aliphatic moiety which contains one or more oxygen, sulfur, nitrogen, phosphorous or silicon atoms;

where an aryl moiety is a mono- or polycyclic unsaturated moiety having 3-14 carbon atoms; and

where a heteroaryl moiety is a mono- or polyheterocyclic unsaturated moiety having 3-14 carbon atoms;

or a pharmaceutically acceptable ~~derivative thereof~~ salt, ester, carbamate, metabolite or pro-drug thereof;

or a pharmaceutically acceptable salt of such ester or carbamate.

42. **(Once amended)** A method for ~~epimerizing the hydroxy group of an aldol moiety~~ producing a compound of claim 1 which comprises contacting a homologous C28 epimer ~~compound containing an aldol moiety~~ with a titanium tetraalkoxide reagent under suitable conditions and for a sufficient time to permit epimerization.

45. **(Once amended)** The method of any of claims 42-44 wherein the ~~aldol-containing~~ homologous C28 epimer ~~compound~~ is rapamycin ~~or a rapamycin derivative or analog~~.